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INCREASED SKIN BLOOD FLOW AND ENHANCED HEAT LOSS IN HUMANS AFTER NIACIN INGESTION

by

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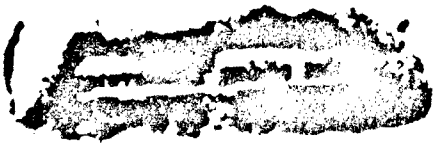

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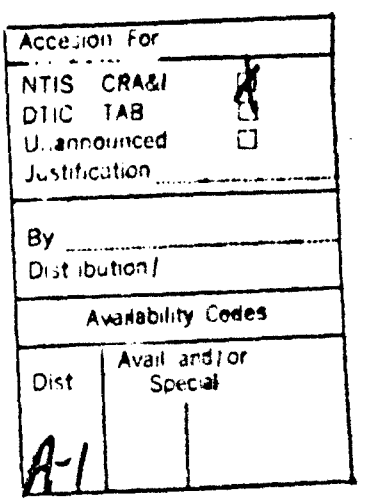

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13 ABSTRACT (Maximum 200 words)

Healthy, young subjects were studied in three separate series of studies characterizing nicotinic acid (NA) ingestion (5 mg·kg^{-1}). 1) At rest, seated (T_a - 30°C, rh = 23%) at 0800 h and again between 1800 and 2100 h. 2) At rest (R) and during seated exercise (X, T_a = 29°C, rh = 30%). 3) During upright exercise when wearing a protective clothing system (T_a = 28°C, rh = 30%). NA treatment resulted in decreased T_{es}, $\dot{T}_{sk}$, SkBF, FBF, heart rate, and cutaneous vascular conductance (CVC) ($P \leq 0.05$). NA decreased mean arterial pressure at rest. Subjects had no difficulty completing seated or upright exercise in either control or NA experiments. The pharmacological manipulation of skin blood flow at rest and during moderate exercise effectively increased sensible heat flux during seated as well as upright exercise. NA ingestion also increased sensible heat flux from individuals dressed in chemical protective clothing. These experiments show that pharmacologic manipulation of skin blood flow by NA ingestion should be done cautiously, especially when NA will be used repeatedly or in novel circumstances.

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

FOREWORD

This report describes a series of studies done at the U.S. Army Research Institute of Environmental Medicine which characterize the physiologic effects of the vasoactive substance nicotinic acid. The responses of humans to ingestion of this vitamin, niacin, was investigated during several different experimental configurations designed to evaluate skin blood flow and heat loss alterations. The associated changes in blood pressure responses and other cardiovascular responses were noted. All experiments were done on healthy, physically active adults. Subject 4 in the circadian and semi-upright exercise experiments admitted that he routinely medicated himself with ibuprofen to diminish pain due to his normal running routine. The responses observed for this subject were diminished compared to those of the other subjects.

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EXECUTIVE SUMMARY

Healthy, young subjects were studied in three separate series of studies characterizing nicotinic acid (NA) ingestion (5 mg•kg^{-1}). 1) At rest, seated (T_a = 30°C, rh = 23%) at 0800 h and again between 1800 and 2100 h. Esophageal temperature (T_{es}), mean weighted skin temperature ($\bar{T}_{sk}$), forearm blood flow (FBF, venous occlusion plethesmography), and skin blood flow (SkBF, laser Doppler velocimetry), mean arterial pressure (MAP) and heart rate (HR) were measured. At both times of day NA treatment resulted in decreased T_{es} and MAP and increased $\bar{T}_{sk}$, SkBF, FBF, heart rate, and cutaneous vascular conductance (CVC) ($p \leq 0.05$). Peak HR at 1800 h was 25 b•min^{-1} higher than at 0800 h ($p \leq 0.05$). MAP decreased an average of 12 Torr in the morning experiments and nearly 16 Torr in the evening experiments. Two of the four subjects experienced severe hypotension after NA treatment at 1800 h. Some diurnal factor, presumably influencing the responsiveness of the cardiovascular system, increased the hypotensive effect of NA at night. 2) At rest (R) and during seated exercise (X, T_a = 29°C, rh = 30%). Peak SkBF and peak FBF were 600% higher in NA rest (NR) than control rest (CR) ($p<0.05$). T_{es} was 0.6°C lower and $\bar{T}_{sk}$ was 0.6°C higher at peak SkBF in NR than CR ($p<0.05$). MAP was 12 Torr lower and HR was 14 b•min^{-1} higher at peak SkBF in NR than CR ($p<0.05$). Both SkBF and FBF were 30% higher and T_{es} was 0.3°C lower during NA exercise (NX) than during control exercise (CX) ($p<0.05$). SkBF and FBF were not different between NR and NX. NA increased SkBF at rest and changed T_{es}, $\bar{T}_{sk}$, HR and MAP accordingly. NA increased SkBF and decreased T_{es} during exercise without significant cardiovascular changes. 3) During upright exercise when wearing a protective clothing system (T_a = 28°C, rh = 30%). Esophageal temperature was significantly lower (0.25°C) after NA ingestion compared to the control experiments. Skin temperatures were higher as a result of increased skin blood flow after NA ingestion. Subjects had no difficulty completing treadmill exercise in either control or NA experiments. Conclusion. The pharmacological manipulation of skin blood flow at rest and during moderate exercise effectively increased sensible heat flux during seated as well as upright exercise. NA ingestion also increased sensible heat flux from individuals dressed in chemical protective clothing. These experiments show that pharmacologic manipulation of skin blood flow by NA ingestion should be done cautiously, especially when NA will be used repeatedly or in novel circumstances.

INTRODUCTION

Nicotinic acid (NA) or niacin is required in the diet to prevent pellagra and other disorders of vitamin deficiency. The physiologically active forms of nicotinic acid are nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both are co-enzymes which catalyze oxidation-reduction reactions. This water-soluble vitamin is used clinically to treat hypercholesterolemia, hypertriglyeridemia and hyperlipoproteinemia (Brown and Goldstein, 1985). One of the unpleasant side effects experienced in patients treated with nicotinic acid is an intense flushing of the skin (Kaijser *et al.*, 1979; Morrow *et al.*, 1989; Phillips and Lightman, 1981; Rolf *et al.*, 1977). Nicotinic acid is thought to dilate the surface vessels near the skin through a prostaglandin-mediated mechanism, as the flush can be inhibited by pre-treatment with sodium salicylate or other inhibitors of prostaglandin synthesis (Kaijser *et al.*, 1979). Hubbard and co-workers (1988, 1989) proposed that the vasodilatory property of NA could be used as a physiologic mechanism to treat heatstroke. Because NA ingestion also markedly decreased mean arterial pressure via dilation of skin surface blood vessels, it was subsequently cautioned that the use of NA as a method to decrease body temperature in heat stroke could be dangerous (Stephenson and Kolka, 1989).

Instead of using a large dose of NA as a treatment for a pathophysiologic condition as Hubbard *et al.* (1988) proposed, we used a smaller dose (300-400 mg) to increase radiative and convective (sensible) heat flux via its known effect on cutaneous vasculature (Brown and Goldstein, 1985; Dipalma and Ritchie, 1977; Gross and Merz, 1948; Mullin *et al.*, 1989) in humans resting in a warm environment (Stephenson and Kolka, 1989). Before NA could be used as a vasodilatory aid in exercising humans, its effects on blood pressure regulation had to be better explored. In particular, the effects of NA on sensible heat flux at different times of day, during seated exercise and during upright exercise in chemical protective clothing were investigated.

Circadian Study

In continuing the investigation of this same dose of niacin (300-400 mg) as a vasodilatory agent, we observed that niacin affects the circulatory system differently at night than in the morning which could result in serious consequences to unwary individuals. This report describes the diurnal differences in the magnitude of the hypotensive response to NA in resting, healthy, young subjects which was observed during a study of the effects of niacin (5 $mg \cdot kg^{-1}$) on thermoregulation. The circadian facet of the study was terminated after two of the four subjects suffered severe hypotension, but the data collected are of interest given the importance of understanding whether NA, as a vasodilating aid, can be used at any time of day.

Seated Exercise Study

Skin flushing caused by nicotinic acid treatment has been studied (Kaijser *et al.*, 1979; Morrow *et al.*, 1989; Phillips and Lightman, 1981; Rolf *et al.*, 1977) and characterized by forearm blood flow measurements (Kaijser *et al*, 1979). The cutaneous vasodilatory action of niacin was quantified by skin blood flow (SkBF) measurements in resting humans in a neutral environment and the resulting increase in sensible heat flux calculated (Stephenson and Kolka, 1989). The anatomical pattern of onset of flushing with niacin ingestion (5 $mg \cdot kg^{-1}$ per os) in that study (Stephenson and Kolka, 1989) was similar to the mantle flushing induced by atropine (Kolka *et al.*, 1984). In a previous study which determined the effects of atropine treatment on thermoregulation (Kolka and Stephenson, 1987), increased SkBF was associated with atropine's anticholinergic action of competitive inhibition of neurotransmission at the sweat gland. Consequently, atropine inhibited insensible heat flux (via wet heat loss) by reducing sweat secretion, but enhanced sensible heat flux (via dry heat loss) by increasing skin blood flow. Therefore, relative thermoregulatory strain during exercise after atropine was higher in moderately warm (Kolka *et al.*, 1986; Stephenson *et al.*, 1988) and hot (Kolka *et al.*, 1984; Kolka *et al.*, 1986) environments. In contrast, niacin increased sensible heat flux by increasing SkBF in seated, resting subjects (Stephenson and Kolka, 1989) without the thermoregulatory liability engendered by pharmacologic inhibition of sweat secretion.

The vasoconstrictor and vasodilator influences and their integration are substantially different between rest and exercise (Johnson, 1986; Rowell, 1986). Consequently, the assumption that NA treatment would enhance sensible heat flux during exercise and reduce thermoregulatory strain may not be valid. Although NA ingestion caused a substantial reduction in mean arterial pressure and increased heart rate in resting subjects (Stephenson and Kolka, 1989), it was not known whether NA treatment had the same cardiovascular effects in exercising man. The initial investigation of how nicotinic acid affected sensible heat flux was done using semi-upright exercise. Not only could the skin blood flow responses be studied better using seated exercise, but the blood pressure responses could be observed without the possible untoward effects of upright exercise. In addition, we constrained the experiments to one time of day (morning).

Upright Exercise and Clothing Study

The time an individual can tolerate work in the heat is decreased by the physical barrier provided by protective clothing systems (Gonzalez *et al.*, 1986; Henane *et al.*, 1979; Muza *et al.*, 1988) and also by the systemic or local administration of pharmaceuticals which impair heat loss (Kolka *et al.*, 1984; Kolka and Stephenson, 1987). Protective clothing systems compromise thermoregulatory heat loss by decreasing the transfer of heat from the body surface via convection and evaporation, thereby increasing heat storage. The microenvironment at the skin surface has a high water vapor content which inhibits evaporative heat exchange, and the physical characteristics of the chemical protective clothing limit dry or sensible heat transfer (Gonzalez *et al.*, 1986). In subjects walking on a treadmill dressed in chemical protective clothing in an environment similar to that used in the present study, work time was decreased compared to experiments in which microclimate cooling was utilized (Muza *et al.*, 1988) or when protective clothing was not worn (Kolka *et al.*, 1986). After observing that exercise after NA ingestion did not affect blood pressure responses, the third series of experiments was initiated to include upright posture and clothing that would require substantial sensible heat flux in order to limit heat storage.

STATEMENT OF PURPOSE

The purpose of the circadian study was to characterize differences in the magnitude of the skin blood flow response to niacin ingestion in resting, healthy, young subjects at two times of day. These two times were chosen because it was expected that any variation would be maximal. The purpose of the seated exercise study was to assess whether the relative vasoconstrictor influence of exercise itself would impact on the cutaneous vasodilatory action of NA observed at rest. A secondary aim of the exercise studies was to determine whether the vasoactive effects of NA treatment during exercise would present additional risks during exercise similar to the sustained tachycardia caused by atropine treatment. The purpose of the clothing study was to ascertain if dry or sensible heat loss could be improved without significant cardiovascular changes during upright low-intensity exercise after NA ingestion when subjects wore protective clothing.

METHODS

PHYSIOLOGICAL MEASUREMENTS

Circadian Study

Four subjects (three men and one woman) volunteered to serve as subjects after they were verbally apprised of the nature and risks of the study. The physical characteristics of the subjects (mean ± standard deviation) were: age: 29 (±5) years; height: 1.72 (±0.05) m; mass: 69.2 (±3.6) kg; and body surface area: 1.79 (±0.05) m^2.

All subjects were completely familiar with all laboratory techniques before the study began. Subjects were studied during rest in a moderately warm environment (T_a = 30°C; 30% rh) while in a seated posture at two different times of day. One experiment was done in the morning at 0800 h and the second experiment was done in the evening between 1800 and 2100 h. The experimental protocol was the same for both experiments. The timing of evening experiments was designed so that the subject was studied approximately 4 h before he/she normally went to sleep at night. The woman was studied in the follicular phase of her menstrual cycle.

Each subject reported to the environmental test chamber after fasting at least 6 h before the experiment. A copper-constantan thermocouple encapsulated in a catheter was swallowed for the measurement of esophageal temperature (T_{es}) and thermocouples (copper-constantan) were attached to the skin at eight sites. The esophageal thermocouple was inserted to a depth of about 25% of the individual's height (Brenglemann, 1987). A mercury-in-silastic strain gauge was placed on the forearm for the measurement of forearm blood flow (FBF) by venous occlusion plethysmography (Hokanson *et al.*, 1975; Whitney, 1953). The strain gauge was placed around a section of forearm distal to the main mass of the muscles to decrease the proportion of muscle in the whole arm cylinder measured. The forearm was suspended (at heart level) by the wrist with a sling apparatus anchored at two points minimizing movement artifact during exercise as the arm and gauge moved in translation with the torso. The measurement of FBF was used as an index of skin

blood flow, even as the forearm blood flow measured included flow through the skin, muscle, adipose tissue and bone (Rowell, 1986). Perfusion of the skin of the forearm, also used as an index of skin blood flow (SkBF), was estimated by laser Doppler velocimetry (Med Pacific, LD6000). Laser probe and strain gauge (for FBF) placement was similar for each experiment for each subject. Heart rate (HR) was measured by electrocardiography (EKG) and arterial pressure was measured by automated auscultation (Accutorr).

After all instruments were attached to the subject, a 15 min control period was initiated. During this period, esophageal and skin temperatures, forearm blood flow and skin blood flow were measured every 0.5 min, and blood pressure and heart rate were measured every 5 min. Five mg niacin per kg body weight was ingested by each subject after the control period. Data were collected after niacin ingestion as was done for the control period for the next 60 to 90 minutes depending on the duration of the NA effect.

Mean skin temperature ($\bar{T}_{sk}$) was calculated as a weighted average of the local skin temperature of the eight sites measured (Nishi and Gagge, 1974):

$$\bar{T}_{sk} = 0.07\ T_{forehead} + 0.175\ T_{chest} + 0.175\ T_{back} + 0.07\ T_{upperarm} + 0.07\ T_{forearm} + 0.05\ T_{hand} + 0.19\ T_{thigh} + 0.20\ T_{calf},\ °C$$

Mean body temperature ($\bar{T}_b$) was calculated from the equation:

$$\bar{T}_b = 0.8\ (T_{es}) + 0.2\ (\bar{T}_{sk}),\ °C$$

Cutaneous vascular conductance (CVC) was calculated from SkBF/MAP (Taylor *et al.*, 1988).

Seated Exercise Study

These same subjects exercised at 50% peak aerobic power (power output = 110 ± 17 W) during two experiments at T_a = 29°C, T_{dp} = 10°C (30% rh). Two other experiments were done at rest. Their peak oxygen utilization was 3.71 (± 0.64) L•min

^{1}. In one experiment (control rest, CR), after instrumentation, resting data were collected for thirty minutes. In a second experiment, 15 minutes of resting data were collected, followed immediately by 30 minutes of seated leg exercise (control exercise, CX). In a third experiment (NR), after 15 minutes of control resting data collection, the subject ingested 5 $mg \cdot kg^{-1}$ nicotinic acid and resting data were collected for 60-75 min. In the fourth experiment (NX), NA was ingested after 15 min rest. When skin blood flow doubled control values (~20 min after niacin ingestion) the subject exercised for 30 minutes. Both resting experiments were done in the days preceding the exercise experiments. Two subjects were studied in niacin experiments first and the remaining two subjects were studied in control experiments first. All experiments were started at 0800 h. Experiments on any subject were completed within 10 days during the late Fall.

For each of the four experiments, the subject sat in a chair positioned behind the cycle ergometer, such that during leg exercise, the legs were parallel to the floor. T_{es}, $\bar{T}_{sk}$, FBF, SkBF and blood pressure were measured as described above under circadian studies. Whole body sweating was determined as the change in body weight from pre- to post-exercise. Heart rate (HR) was measured from the EKG record.

Upright Exercise and Clothing Study

Four healthy adults (two male and two female) exercised at 40-50% maximal aerobic power during two separate experiments at T_a = 28°C, T_{dp} = 4°C. In one experiment (control, C), after instrumentation, 15 minutes of resting data were collected followed immediately by 30 minutes of treadmill exercise. In the second experiment (N), after 15 minutes of control data collection each subject ingested 5 $mg \cdot kg^{-1}$ NA. After skin blood flow, measured on the upper back, had doubled (~10-15 min), the subject exercised for 30 minutes. Experiments on any subject were completed within 5 days during the early Winter.

Upon arriving at the laboratory for each experiment, the subject was instrumented for T_{es} and $\bar{T}_{sk}$ as described above for the circadian study. Whole body sweating was determined as the change in body weight from pre- to post-exercise. Oxygen consumption was measured by an automated method (SensorMedics) at rest and after

15 minutes of exercise. Cardiac output was estimated from a CO_2 rebreathing method at rest and after 20 minutes of exercise. Skin blood flow or cutaneous vascular perfusion was measured over muscle on the upper back on the midline between the scapulae, over muscle and not bone tissue by laser Doppler velociometry. After instrumentation, each subject dressed in the standard battle dress uniform, and chemical protective clothing, MOPP II (Mission Oriented Protective Posture; mask, hood and gloves not worn). The characteristics of this clothing ensemble have been described as the insulative and permeation characteristics as Clo = 1.44 and i_m = 0.30, respectively. After complete instrumentation and dressing, a rest period began. If a control experiment was done, 30 min of low to moderate exercise followed. If a drug experiment was done, the subject ingested the appropriate dose of NA. Data collection continued during this period. When blood flow to the skin of the upper back was double that of the control experiment, an identical exercise period began.

STATISTICAL ANALYSES

The diurnal variation in pre-treatment T_{es}, $\bar{T}_{sk}$, MAP, HR, SkBF, FBF and CVC was analyzed by a one way analysis of variance with repeated measures. Other data were analyzed by a two way analysis of variance with repeated measures, with the factors being experimental time (pretreatment (A1), niacin treatment when FBF was at a peak (A2) and niacin treatment when T_{es} was minimal (A3)) and time of day (0800 (B1) and 1800 (B2) h). Tukey's tests of critical differences were performed when appropriate ($p<0.05$).

In the exercise experiments (including the controls for rest and clothing experiments), temperatures, all data were analyzed by ANOVA (drug by time) with repeated measures. Tukey's tests of critical differences were performed when appropriate ($p<0.05$).

RESULTS

Circadian Study

Table 1 shows the pretreatment means in esophageal temperature, mean skin temperature, skin blood flow, forearm blood flow, mean arterial pressure, heart rate and cutaneous vascular conductance at the two times of day. T_{es} and $\bar{T}_{sk}$ increased 0.4 ($p<0.05$) and 0.6°C respectively at 1800 h compared to 0800 h. In the evening experiment skin blood flow increased 47% ($p<0.05$) compared to the morning experiment. Although forearm blood flow was 115% greater in the evening, this difference was not statistically significant. Both heart rate and mean arterial pressure were greater in the evening than in the morning, but this difference was not statistically significant. CVC was significantly increased in the evening and was 43% greater ($p<0.05$) than in the morning.

Table 1. Mean (±SD) pretreatment data at 0800 h and 1800 h.

Variable	0800 h	1800 h	p value
T_{es} (°C)	36.6 (0.3)	37.0 (0.2)	0.03
$\bar{T}_{sk}$ (°C)	33.9 (0.3)	34.5 (0.4)	0.09
SkBF (mV)	23.1 (8.0)	33.9 (11.5)	0.02
FBF ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$)	2.6 (1.2)	5.6 (3.9)	0.30
HR ($beats \cdot min^{-1}$)	52 (8)	57 (7)	0.12
MAP (Torr)	85 (3)	89 (7)	0.14
CVC ($mV \cdot Torr^{-1}$)	28.5 (9.5)	40.7 (12.9)	0.01

The onset time for NA effects was not significantly different at the two times of day, but depended on the individual and averaged 18.6 (±4.8) min at 0800 h and

14.5 (±3.3) min at 1800 h. Because of this individual variability the experimental data were compared statistically during pretreatment, at the time of maximal cutaneous vasodilation in the forearm and when T_{es} was minimal or when the individual response was maximal.

The time course of the physiologic responses to NA at the two times of day are shown for one subject in Figs. 1-3. T_{es} and $\bar{T}_{sk}$ are shown in Fig. 1. The rapid change in T_{es} between 15 and 20 min of the experiments was due to the cooling effect of drinking water (30-50 ml) after taking the drug. $\bar{T}_{sk}$ increased dramatically at 0800 h after the drug was taken, but at 1800 h the relative change in $\bar{T}_{sk}$ was not as great even though the absolute mean skin temperature was nearly the same as in the morning. During the experiment at 1800 h the subject felt light-headed and dizzy[1] at about 45 min (45 min after taking the drug). At 62 min the venous occlusion plethysmographic measurements were discontinued (Fig. 2) and the subject's body position was changed from a seated to a supine posture. All other data collection continued. The change in posture was accompanied by a transient increase in T_{es}. SkBF also increased dramatically when the subject assumed the supine posture. Fig. 3 shows the response of mean arterial pressure and heart rate during the two experiments.

Table 2 compares the average responses of the four subjects at three different times during the two experiments. The mean data show similar responses to NA treatment as shown for Subject 1 (Figs. 1-3). Esophageal temperature decreased by 0.6°C at 0800 h and 0.5°C at 1800 h after niacin treatment and $\bar{T}_{sk}$ increased by 0.7 and 0.5°C at 0800 and 1800 h respectively. Mean body temperature decreased 0.5°C in the morning experiment, but only decreased by 0.3°C in the evening experiment. SkBF increased by about 500% after NA treatment during the 0800 h experiment, but during the 1800 h experiment only increased 407%. However, the absolute SkBF was higher at 1800 h than at 0800 h. The FBF response was similar with the relative

[1]Subject 2 experienced dizziness and tunnel vision which was severe enough to warrant termination of the experiment. His mean arterial pressure fell to 59 Torr at one point before he was placed in a supine position and a cold towel was placed on his neck. He remained supine for approximately 40 min. SkBF had increased by 436 % to 150 mV from an initial value of 28 mV before severe hypotension occurred and FBF responded similarly to SkBF. Resting SkBF and FBF were greatly increased at 1800 h compared to 0800 h in this subject as was CVC.

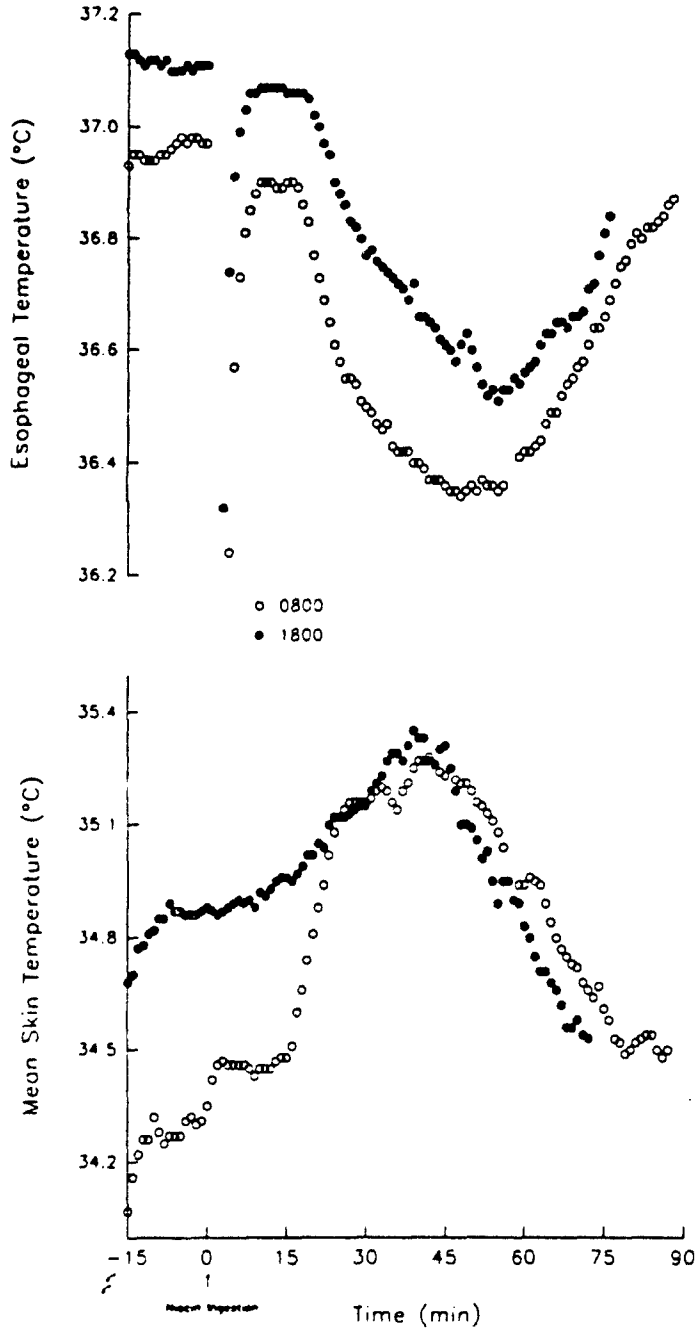

Figure 1. Esophageal and mean skin temperature as function of experimental time (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 0 min. The drink transiently cooled the esophageal thermocouple.

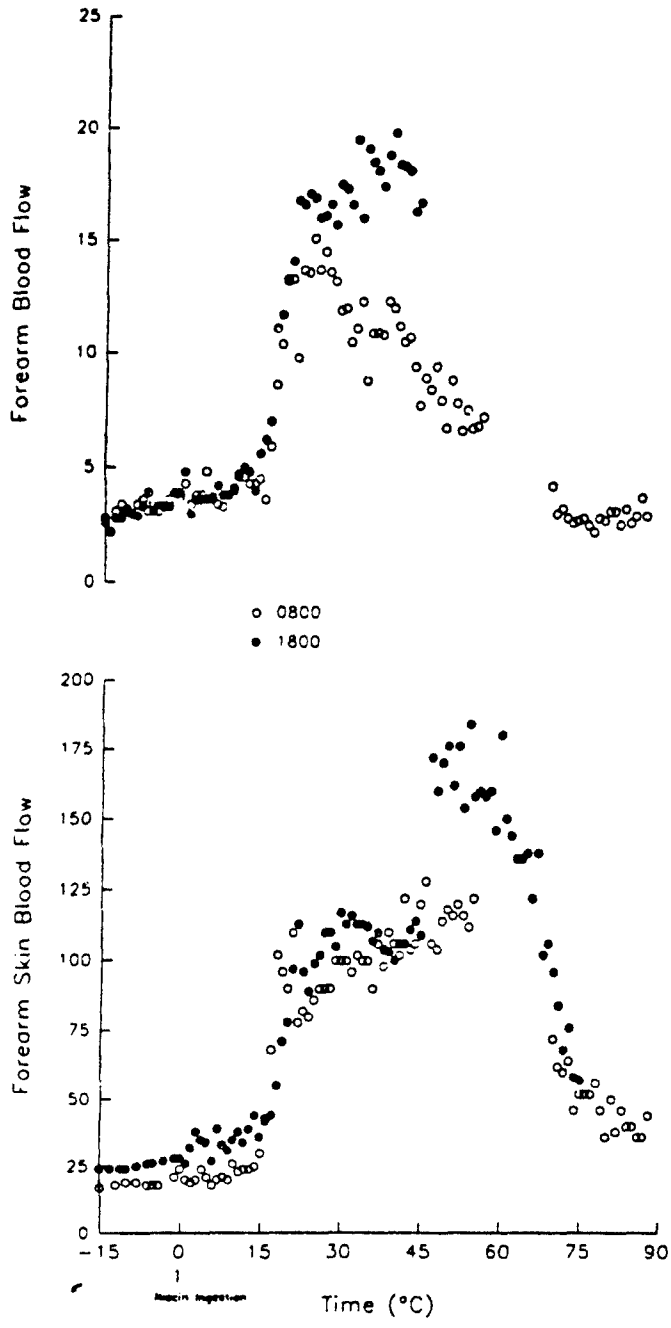

Figure 2. Laser Doppler flow as an index of skin blood flow and forearm blood flow as a function of experimental time (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 0 min.

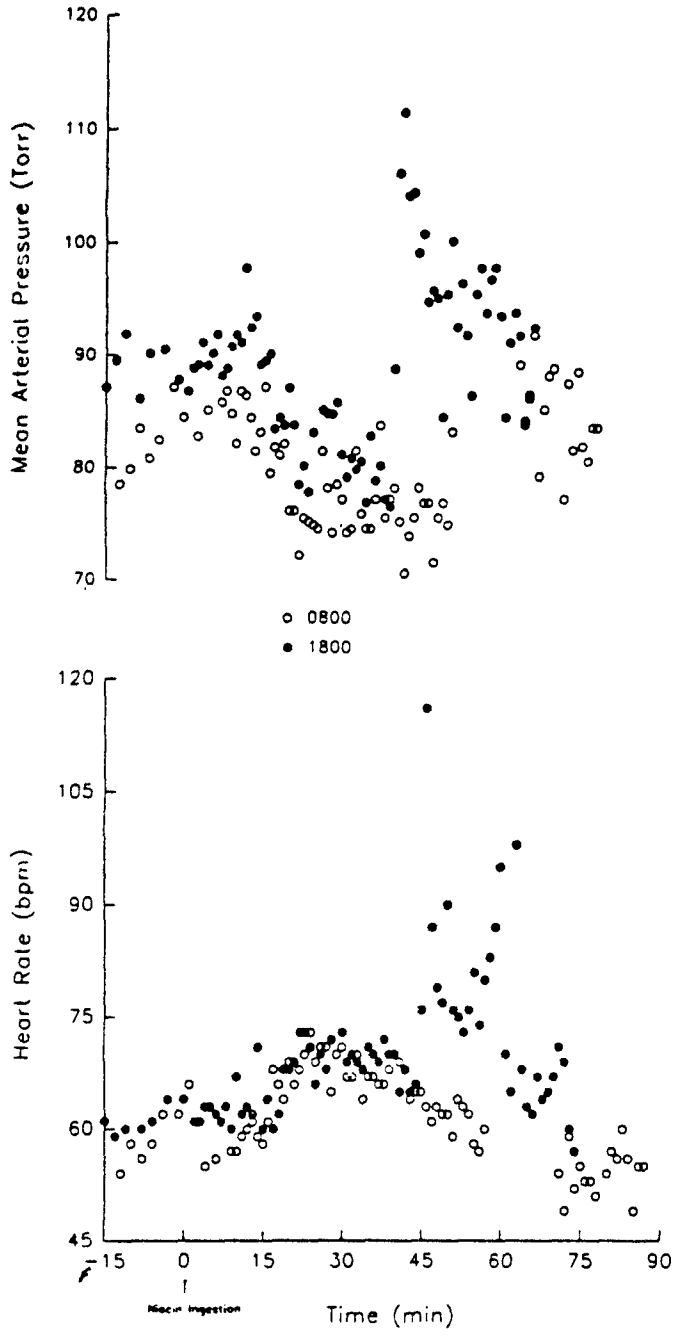

Figure 3. Mean arterial pressure (MAP) and heart rate as a function of experimental time (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 0 min.

increase in FBF being greater in the morning than in the evening, but the absolute FBF was greater at 1800 h. Mean arterial pressure decreased by about 12 Torr in the morning experiment after niacin treatment and nearly 16 Torr in the evening experiment. The peak heart rate was also greater after NA treatment during the evening experiment than the morning experiment and the difference was 25 beats•min^{-1}. The CVC at the highest SkBF was 209.7 mV•Torr^{-1} at 0800 h and 271.9 mV•Torr^{-1} at 1800 h, but there was no significant difference between the two times (p=0.09). CVC increased after niacin treatment by an average of 635% in the morning and by 568% in the evening, but the peak CVC averaged 82.2 mV•Torr^{-1} greater at 1800 h than at 0800 h.

Seated Exercise Study

All subjects completed all experiments without difficulty. The response to NA ingestion at rest is shown in Figure 4. Typically, the NA dilation at rest was significantly reduced by 75 minutes after ingestion (Figure 4). Data from CR after equilibration to the environment are presented in Table 3. In NR, approximately 10-20 minutes after niacin ingestion the onset of measurable vasodilation was observed. This vasodilation was first apparent on the face and neck and moved peripherally and caudally. The vasodilation dissipated after approximately 60 minutes. At rest, peak SkBF and FBF were 600% higher after NA ingestion compared to control (Table 3). $\bar{T}_{sk}$ was 0.6°C higher in NR compared to CR. T_{es} was 0.6°C lower in NR than CR. MAP at rest after NA ingestion was 12 Torr lower than CR, consequently HR was 14 b•min^{-1} higher in NR.

During exercise, SkBF averaged 350% higher and FBF averaged 500% higher in CX than CR (Table 3). During (NX), exercise SkBF averaged 500% higher and FBF averaged 700% higher than CR. A typical skin blood flow response to exercise after NA ingestion is shown in Figure 5. Niacin was ingested at time = 0 in the exercise experiment. Exercise began when resting skin blood flow doubled (11.5 min in this example); control exercise data are presented from the start of exercise (11.5 min) on this figure for comparative purposes. Oxygen uptake was not different during exercise between experiments and averaged 1.78 (± 0.27) L•min^{-1}.

Table 2. Data presented are means (±SD) where factor A is experimental time and factor B is time of day before niacin treatment (A1), after peak response of FBF to niacin (A2), and after maximal response of T_{es} to niacin (A3) during the 0800 h (B1) and 1800 h (B2) experiments.

	0800 h (B1)			1800 h (B2)	
A1	A2	A3	A1	A2	A3
T_{es} (°C) 36.6 (0.3)	36.2 (0.3)	36.0 (0.4)	37.0 (0.2)	36.6 (0.2)	36.5 (0.2)
A1>A2>A3 $p<0.05$; B1<B2 $p<0.05$					
$\bar{T}_{sk}$ (°C) 33.9 (0.3)	34.5 (0.3)	34.6 (0.4)	34.5 (0.4)	34.9 (0.7)	35.0 (0.6)
A1<A2<A3 $p<0.05$; B1=B2 $p=0.29$					
$\bar{T}_b$ (°C) 36.1 (0.3)	35.9 (0.3)	35.8 (0.3)	36.5 (0.2)	36.3 (0.3)	36.2 (0.3)
A1>A2>A3 $p<0.05$; B1<B2 $p<0.05$					
SkBF (mV) 23 (8)	123 (67)	138 (51)	34 (12)	172 (66)	155 (77)
A1<A2, A1<A3 $p<0.05$; B1=B2 $p=0.28$					
FBF 2.6 (1.2)	17.6 (4.3)	10.9 (3.1)	5.6 (3.9)	21.2 (8.1)	11.9 (5.5)
A1<A2, A1<A3, A2>A3 $p<0.05$					
MAP (Torr) 81 (3)	72 (4)	69 (2)	84 (7)	81 (6)	68 (9)
A1>A2>A3 $p<0.05$; B1=B2 $p=0.26$; AxB $p=0.06$					
HR 52 (8)	60 (6)	66 (6)	57 (7)	72 (17)	91 (22)
A1<A2, A1<A3 $p<0.05$; B1<B2 $p<0.05$					
CVC 29 (9)	173 (97)	182 (76)	41 (13)	217 (91)	234 (81)
A1<A2, A1<A3 $p<0.05$; B1=B2 $p=0.18$					

Skin blood flow averaged 30% higher (Table 3) during exercise after niacin ingestion than during control exercise experiments. The higher skin blood flow was similarly measured by laser Doppler velociometry or venous occlusion plethysmography. Increased blood flow to the skin surface increased radiative and convective heat flux during exercise after niacin ingestion thereby decreasing esophageal temperature during exercise compared to control experiments (Table 3). Higher skin blood flow and subsequent dry heat loss decreased both the rate of heat storage ($0.11\pm0.01°C\cdot min^{-1}$ (CX) vs. $0.07\pm0.03°C\cdot min^{-1}$ (NX)) , and total heat storage as indicated by the absolute change in T_{es} during exercise after NA ingestion ($0.60\pm0.29°C$ (CX) vs. $0.34\pm0.20°C$ (NX)). Whole body sweating rate was 60% lower in NX ($6.9\pm1.4\ g\cdot min^{-1}$) compared to CX ($17.4\pm4.1\ g\cdot min^{-1}$) as the core temperature (T_{es} in these experiments) drive for evaporative heat loss was lower. Forearm vascular conductance and cutaneous vascular conductance data show the effect of NA on skin blood flow (Table 4) during rest and exercise.

Table 3. Mean (± SD) thermal and cardiovascular variables for four subjects at peak skin blood flow at rest (R) or averaged during exercise (X) in control experiments (C) and after niacin ingestion (N).

	CR	NR	CX	NX
SkBF, mV	23 (8)	159 (63)*	105 (32)†	140 (29)*
$\bar{F}$BF, $ml\cdot100ml^{-1}\cdot min^{-1}$	2.6 (1.2)	17.6 (4.3)*	16.4 (4.7)†	21.6 (5.1)*
T_{es}, °C	36.62 (0.27)	36.03 (0.36)*	37.17 (0.28)†	36.90(0.30)*†
$\bar{T}_{sk}$, °C	33.93 (0.29)	34.53 (0.43)*	33.69 (0.47)	33.83 (0.43)†
HR, $b\cdot min^{-1}$	52 (8)	66 (6)*	121 (10)†	120 (5)†
MAP, Torr	81 (3)	69 (2)*	98 (5)†	97 (6)†

CR, control rest; NR, niacin rest; CX, control exercise; NX, niacin exercise.
*Different from control, $p<0.05$.
†Different from rest in the same treatment. NX < NR, NX > NR or CX > CR, $p<0.05$.

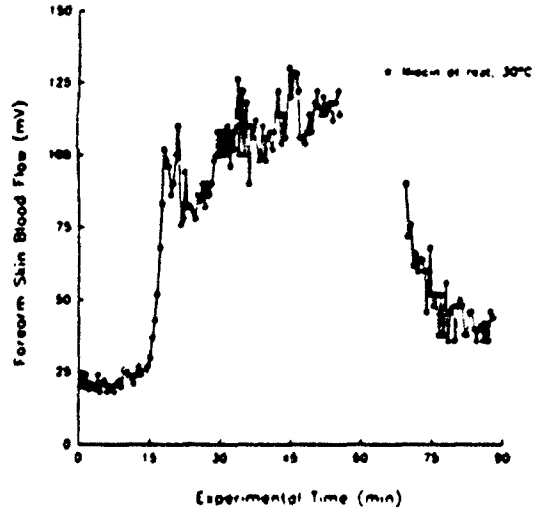

Figure 4. Laser Doppler flow as an index of skin blood flow as a function of experimental time in resting experiments for a representative subject.

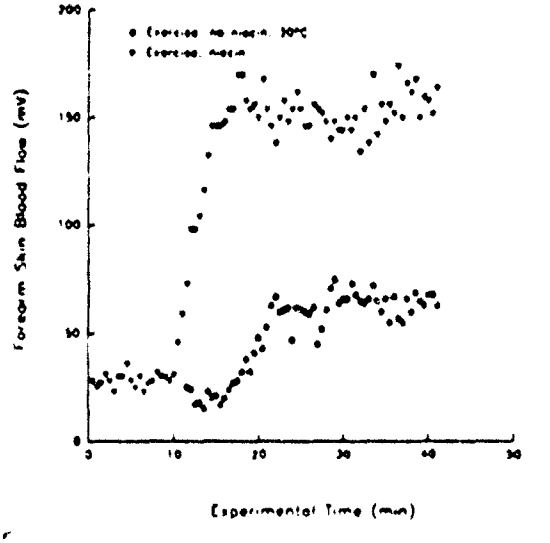

Figure 5. Laser Doppler flow as an index of skin blood flow as a function of experimental time in an exercising subject in both control experiments and after niacin ingestion.

Table 4. Mean (± SD) cardiovascular indices at peak skin blood flow at rest or during exercise for the four subjects in both experiments.

	CR	NR	CX	NX
FVC (ml•100ml^{-1}•min^{-1}•100mm Hg^{-1})	3.2 ± 1.4	24.9 ± 7.0*	16.7 ± 4.5†	22.6±6.0*
CVC (Mv•100mm Hg^{-1})	29 ± 9	173 ± 97*	107 ± 15†	145 ± 17*

FVC, forearm vascular conductance, calculated as forearm blood flow divided by mean arterial pressure.
CVC, cutaneous vascular conductance, calculated as skin blood flow divided by mean arterial pressure.
* Niacin different from Control, $p<0.05$
† Different from rest in the same treatment, $p<0.05$

Upright Exercise and Clothing Study

All subjects, when wearing the clothing system, completed thirty minutes of treadmill exercise without difficulty in both the control and the niacin experiments. The average increase in esophageal temperature during exercise in the control studies was 0.5°C compared with 0.2°C in the niacin studies. This response is shown in Figure 6 as mean T_{es} for the four subjects. Various cardiovascular variables measured during these experiments are shown in Table 5. There were no significant differences in oxygen utilization, cardiac output, heart rate and stroke volume between control experiments and NA experiments. Figures 7 and 8 show the average chest and forearm temperatures during the control and niacin experiments at rest and during treadmill walking. The sustained increase in both chest and forearm skin temperature shows that greater dry heat loss was possible during the niacin experiments compared to the control experiments (Figs. 7 and 8). Skin temperature differences between the control and NA experiments were calculated for the chest (Fig. 9) and forearm (Fig. 10). It is evident that NA increased chest and skin blood flow which caused increased skin temperatures on the chest and the forearm which were sustained during exercise, thereby increasing sensible heat flux.

Table 5. Mean (± SD) cardiovascular variables for four subjects at rest (R) or during treadmill exercise (X) wearing the clothing system in control experiments (C) and after niacin ingestion (N).

	CR	NR	CX	NX
VO_2, L•min^{-1}	0.27 (0.02)	0.30 (0.04)	1.30 (0.17)	1.31 (0.14)
Q_c, L•min^{-1}	4.7 (0.8)	5.1 (0.9)	11.6 (1.7)	11.9 (2.9)
HR, b•min^{-1}	70 (12)	75 (6)	124 (25)	137 (22)
V_c, ml•b^{-1}	70 (22)	69 (16)	98 (29)	90 (32)

CR, control rest; NR, niacin rest; CX, control exercise; NX, niacin exercise. VO_2, oxygen consumption; Q_c, cardiac output; HR, heart rate; V_c, cardiac stroke volume.

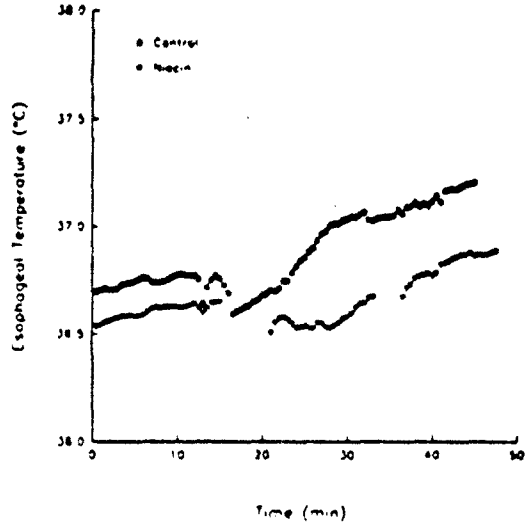

Figure 6. Mean esophageal temperature for four subjects during treadmill walking when wearing protective clothing in control experiments and after niacin ingestion.

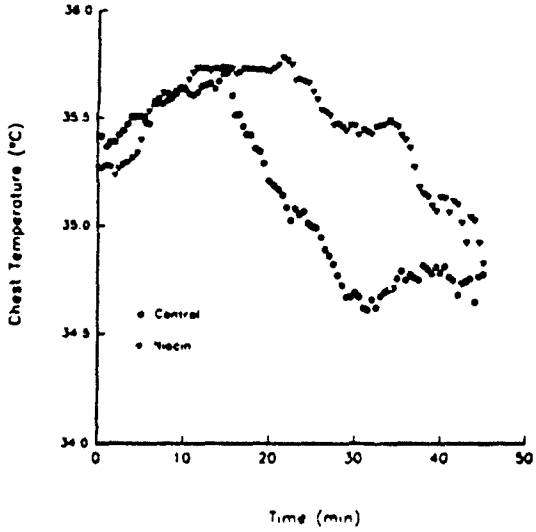

Figure 7. Mean chest temperature under the clothing for four subjects during treadmill walking in control experiments and after niacin ingestion.

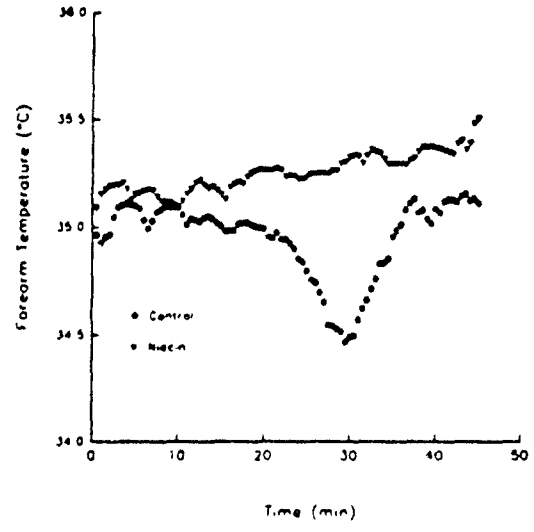

Figure 8. Mean forearm temperature under the clothing for four subjects during treadmill walking in control experiments and after niacin ingestion.

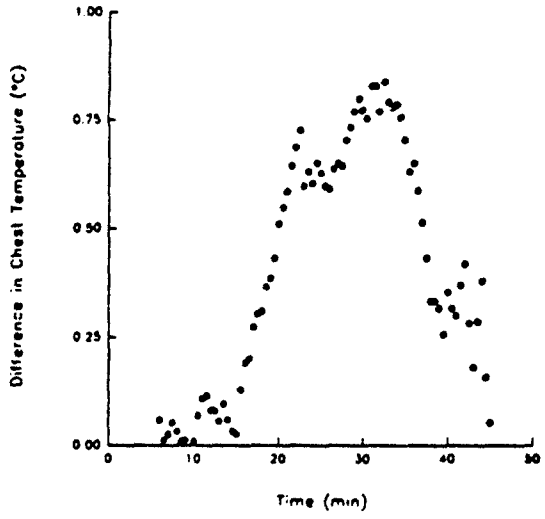

Figure 9. The average difference in chest temperature under the clothing for four subjects between niacin experiments and control experiments.

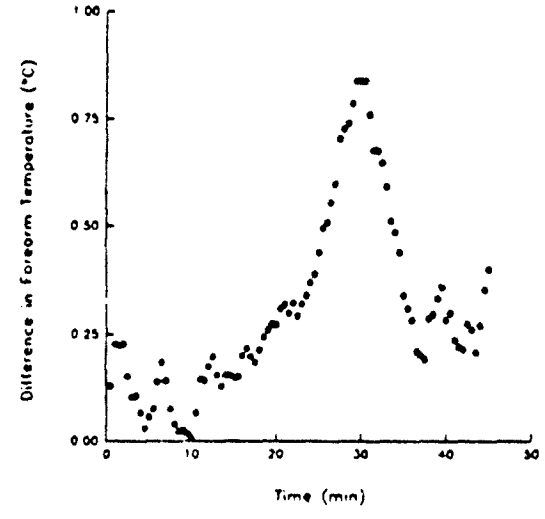

Figure 10. The average difference in forearm temperature under the clothing for four subjects between niacin experiments and control experiments.

DISCUSSION

Circadian Study

Circadian rhythms in most, if not all, parameters affecting cardiovascular function are known. At least partly, these reflect biological rhythms in the central nervous system (Lydic, 1989). In particular, autonomic neurotransmitters which directly affect vascular tone, such as epinephrine and norepinephrine (Akerstadt and Levi, 1982; Prinz *et al.*, 1979; Stene *et al.*, 1980) are on the rise in the morning hours and reach a peak in early afternoon. Forearm blood flow, as measured by venous occlusion plethysmography, varies as a function of time of day (Kaneko, *et al.*, 1968; Smith, 1969). Most recently, Panza *et al.* (1991) have confirmed that FBF is lower in the morning than the afternoon and evening. Neural or neuroendocrine biological rhythms may be the basis for the observed circadian rhythms in FBF, heart rate (Kleitman and Ramsaroop, 1948; Halberg, 1968) and blood pressure (Athanasiadis *et al.*, 1969, Wang, *et al.*, 1992). The incidence of cardiovascular ischemic events is increased in the morning and Quyyumi *et al.* (1992) proposed that an underlying circadian mechanism for ischemic events was greater coronary resistance in the morning. Panza *et al.* (1991) have reported that basal vascular tone is greater in the morning (0700 h) than at 1200 h or 1900 h. Alpha-adrenergic antagonism in the morning caused a greater decrease in vascular resistance than either the afternoon or evening. It was demonstrated (Panza *et al.*, 1991) that circadian oscillation in vascular resistance and blood flow could be abolished by infusion of an alpha-adrenergic antagonist. Taken together the studies cited above indicate that circadian variation in neural or neural effector output can modulate cardiovascular effector function in humans such that effector function exhibits circadian variation. Thus, cardiovascular circadian variation in response to NA ingestion was anticipated. However, to consider a vasodilatory compound as a thermoregulatory aid to increase sensible heat flux in an appropriate environment (Tsk > Ta) differential circadian effects of the compound must be assessed.

The results from the current study suggest that there is a troublesome side effect of niacin administered per os to healthy volunteers in the evening. In addition to the marked cutaneous vasodilation and decreased mean arterial pressure which also

occurred at 0800 h (Table 2), niacin treatment at 1800 h evoked severe hypotension in two of four subjects.

Mean arterial pressure decreased by 15% at 0800h and decreased more (19%) in the experiment at 1800 after niacin treatment, although this observation was not statistically significant (B1=B2, p=0.26; AxB interaction = 0.06, Table 2). We could not show statistically that the severity of hypotension was more pronounced during the experiment at 1800 h than at 0800 h for two reasons. First, the investigators and medical staff had to interrupt data collection to counteract the hypotensive effect of NA in two subjects. In one of these (Subject 2), no data were collected after that. Second, the counteractive measures were to place a cold compress against the neck of the subjects and to change them from seated to a supine position. Also, the feet of one subject (Subject 2) were raised above the level of the heart. These counteractive measures effectively increased mean arterial pressure (Fig. 3). However, because these experiments took place in a research laboratory and not in a clinical situation, we deemed to report the results on only four subjects rather than continue the study. Because the subject number was small (n = 4), the probability of committing a type II error is relatively high, and the power of the test is reduced.

Mean arterial pressure decreased more in the other two subjects in the experiment at 1800 h than at 0800 h, although they did not experience symptoms of extreme hypotension. In one of these subjects (Subject 4) the magnitude of the SkBF response to niacin treatment was about equal in the two experiments, although SkBF at 1800 h was greater than at 0800 h in the other subject. Subjects 3 and 4 tolerated the more pronounced decrease in mean arterial blood pressure after niacin treatment at 1800 h compared to 0800 h and peak heart rate with niacin treatment for the two subjects respectively was 17 and 4 beats•min^{-1} higher at 1800 h than at 0800 h. On the other hand, the peak heart rates of Subjects 1 and 2, respectively, after niacin treatment was 45 and 32 beats•min^{-1} higher in the evening than in the morning. Subjects 3 and 4 were highly trained runners and their highly trained condition may have contributed to their tolerance (Rowell, 1986). However, Subjects 1 and 2 were both in an exercised-trained state, although their maximal aerobic power was less than Subjects 3 and 4. Also Subjects 3 and 4 were younger than the other two subjects. Finally, the responses of Subject 4 should be examined carefully as he admitted to

routinely medicating himself with therapeutic doses of ibuprofen to decrease the sensation of pain after his daily workout. Unfortunately, the investigators did not know of this practice until after these experiments were completed. It is completely plausible that the routine use of ibuprofen impacted on the SkBF responses of Subject 4, as discussed below.

The physiologic explanation for the more severe decrease in mean arterial pressure during niacin treatment at 1800 h compared to 0800 h is not yet clear. There is circadian change in the vasoconstrictor responsiveness of the cardiovascular system (Panza *et al.*, 1991) which may contribute to the greater hypotensive effect of niacin at night. Whether the increased SkBF in the afternoon and evening (Table 1, $p=0.02$) is the result of diminished vasoconstrictor activity or another factor contributing to the greater hypotensive effect of NA ingestion at night is not known, although modification of skin blood flow is an integral part of the circadian rhythm in the control of thermoregulation (Stephenson *et al.*, 1984). The increased CVC before niacin treatment at 1800 h compared to 0800 h is further indication that cardiovascular responsiveness was different at the two times of day.

There is some evidence that the vasodilatory mechanism of action of nicotinic acid is via a prostanoid intermediary. Kaijser *et al.* (1979) reported that indomethacin significantly reduced the forearm blood flow response to nicotinic acid. Another study showed that indomethacin was more effective than benorylate, a less potent prostaglandin synthetase inhibitor, in reducing the skin temperature response to nicotinic acid (Phillips and Lightman, 1981). It has also been reported that prostaglandin excretion was increased two days after initiation of niacin treatment in hyperlipidemic women (Olsson *et al.*, 1983), although prostaglandin excretion was at control level again after 28 days of treatment. It was noted that flushing in response to the drug had also abated by that time. PGI_2, which has direct action on vascular smooth muscle cells, has been postulated to be the vasodilatory intermediary of nicotinic acid (Olsson *et al.*, 1983). However, a more recent report (Morrow *et al.*, 1989) indicated that PGD_2 was the most likely prostaglandin mediator of the vasodilatory action because a metabolite of PGD_2, 9α- 11β-PGF_2, increased in the plasma of volunteers and reached maximal concentration around the time of maximal flushing after ingestion of 500 mg of nicotinic acid.

The apparent diurnal variation of the effect of NA on cardiovascular responses is another example of the effects of biological rhythms on medicine (Reinberg and Smolensky, 1983) and could be due to diurnal variation: 1) in the synthesis of the prostanoid or other vasodilatory compound with NA treatment so there is a greater amount of the vasodilatory compound to act on available smooth muscle receptors; 2) in the affinity of the vasodilatory compound for the vascular smooth muscle receptor (Nicosia and Patrono, 1989); 3) in vasodilatory compound receptor number, signal processing or placement; 4) in the clearance of the vasodilatory component; and 5) in a waning vasoconstrictor influence (Panza *et al.*, 1991) which modulates vasodilatory action.

The method of niacin treatment used in the current study was different than that used in the clinical situation. First, the human volunteers were healthy and ingested the drug after fasting at least 6 h, while in the clinical situation, niacin is usually taken with meals. Also, aspirin or some other prostaglandin synthetase inhibitor is combined with niacin therapy to moderate the degree of cutaneous flushing in the clinical situation. The dose of niacin in the current study was 5 $mg \cdot kg^{-1}$ or between 300 and 400 mg. Anywhere from 1-7 g might be given daily in the clinical situation. Also, the environmental conditions of the test chamber simulated a summer day (30°C) with 29% relative humidity. The $\bar{T}_{sk}$ averaged 33.9 and 34.5°C at 0800 and 1800 h, respectively. It may be that the cutaneous vasodilatory response to niacin would be less when ambient temperature and $\bar{T}_{sk}$ were less. Livingstone and Kuehn (1981) were unable to detect changes in $\bar{T}_{sk}$ as measured by infrared thermometry after niacin treatment in subjects placed in an ambient temperature of 25°C, although they did observe the characteristic flushing of the skin. Also, core temperature and skin temperature were not different from control experiments when nicotinic acid was administered to subjects prior to exposure to ambient temperature of 10°C (Doi, *et al.*, 1979). Heart rate and blood pressure were also unaffected by nicotinic acid treatment in the cold environment. In addition, the subjects in the current investigation remained in the seated posture throughout the experiment. Individuals may remain in a seated posture for an hour or longer in certain jobs, while driving a vehicle, or even while viewing television or a movie. In other situations, individuals will be fairly active and exercise will increase MAP and decrease the probability of an hypotensive episode. Finally, the drug was purposefully given to subjects in the current investigation when

it was anticipated that core temperature was near its circadian peak. It may be that the severe hypotensive episodes which we report in the current study are only possible if niacin is ingested in a warm environment while the individual is fasting and not physically active. Nevertheless, the cutaneous vasodilatory effect of niacin and the resultant decreased mean arterial pressure is an indication that NA used as a vasodilatory aid presents a potential danger if used indiscriminately at any time of day. Further research is necessary to describe the circadian variation in SkBF to titrate an effective, yet safe, niacin dose.

Seated Exercise Study

These studies show that an oral dose of nicotinic acid ingested approximately 20 min before exercise in a neutral environment increased skin blood flow during seated cycle exercise. Exercise after nicotinic acid ingestion did not increase skin and forearm blood flows above that observed at rest after nicotinic acid, yet SkBF and FBF were higher than during exercise in the control condition. The rate of heat storage as measured by esophageal temperature was attenuated after nicotinic acid ingestion, which decreased sudomotor activity and whole body sweating. Therefore, during exercise, the contribution of dry or sensible heat flux was greater and insensible (that due to sweating) heat flux was lower after nicotinic acid ingestion. These observations indicate that the vasodilatory effect of nicotinic acid persisted during seated exercise.

This study is another example of pharmacological manipulation of the thermoregulatory system such that marked drug-induced cutaneous vasodilation results in lower core temperatures which decreases the stimulus for sweat secretion. Previously, we reported the uncoupling or disassociation of the thermoregulatory effectors, cutaneous vasodilation and sweating, during exercise in a cool environment after atropine treatment (Kolka *et al.*, 1989) and postulated that local vasodilatory factors promoted vasodilation because the neural stimulus for sweating had been reduced in response to decreasing esophageal temperature. This phenomenon was also observed in the current experiments after nicotinic acid ingestion. The persistent cutaneous vasodilation despite reduced core temperature drive for heat loss is an indication that skin blood flow was not modulated by efferent activity controlling

sweat secretion after niacin treatment. Alternately, the persistent cutaneous vasodilation in the current study may indicate that neural modulation is overridden, or that the mechanism driving cutaneous vasodilation is due to local factors (Burnstock, 1985; Furchgott and Zawadski, 1980; Griffith *et al.*, 1988) such as PGD_2 (Morrow *et al.*, 1989), PGI_2 (Olsson *et al.*, 1983) or nitric oxide (NO) and is not responsive to the thermoregulatory controller. In humans, active cutaneous vasodilation in response to body heating is thought to be cholinergic, although cholinergic vasodilatory fibers have not been definitely identified (see Rowell, 1986 for review). However, other vasodilatory substances, neurotransmitters or neuromodulators other than acetylcholine may contribute to skin vasodilation during exercise. Potent endogenous vasoactive agents which act through NO, as well as nonadrenergic, noncholinergic neurotransmitters and neuromodulators of smooth muscle function (Burnstock, 1985; Furchgott and Zawadski, 1980), any combination of which may contribute to the control of skin blood flow in humans. Recent work by Dietz *et al.* (1994) has shown the importance of NO as a neuromodulator of SkBF.

The increased sensible heat flux (through increased SkBF) and reduced insensible heat flux (through lower sweating) during exercise after nicotinic acid ingestion is similar to other studies in which skin blood flow had been increased by another vasoactive agent, atropine (Kolka *et al.*, 1984; 1986). However, the mechanism of action may be different between the two drugs. Although the mechanism of the vasodilatory action of atropine is not established, it has been speculated to be a property of co-release of the neurotransmitters VIP and Ach at the neuroeffector junction of the sweat gland (Kolka and Stephenson, 1987). More recent research has discounted the importance of VIP in the neural control of SkBF (Savage, *et al.*, 1990). The vasodilatory action of nicotinic acid is a prostaglandin-mediated mechanism as aspirin inhibits the flushing (Moncada *et al.*, 1985). The prostanoid mediating vasodilation may be prostacyclin (PGI_2) because infusion of PGI_2 at rest (Szczeklik *et al.*, 1978; O'Grady *et al.*, 1980) shows a similar vasodilatory response to nicotinic acid ingestion at rest (Stephenson and Kolka, 1989). PGI_2 is also the major prostaglandin synthesized in the blood vessel endothelium (Dusting *et al.*, 1979). However, a recent report showed a correlation between increasing blood levels of the major metabolite ($9\alpha 11\beta$-PGF_2) of prostaglandin D_2 (PGD_2) and skin flushing duration and intensity after nicotinic acid ingestion (Morrow *et al.*, 1989).

Another aim of this study was to assess whether the relative vasoconstrictor influence inherent in exercise (Johnson, 1986; Rowell, 1986) would impact on the cutaneous vasodilatory action of niacin. A transient vasoconstriction usually occurs at exercise onset which has been attributed to either a neurogenic mechanism or one involving catecholamine release (Johnson, 1986; Johnson and Park, 1982; Rowell, 1986). In addition, maximal skin blood flow during exercise, especially during upright exercise, is lower than that seen during supine exercise with whole body and/or local heating (Johnson, 1986; Rowell, 1986). Exercise itself, elicits vasoconstrictor activity. Recently, Kellogg and colleagues using bretylium, which blocks presynaptic norepinephrine release, showed higher skin blood flow during exercise compared to control studies indicating the presence of vasoconstrictor activity in the skin vascular beds (Kellogg *et al.*, 1991). During exercise, in the control experiments, the vasoconstrictor response at the onset of exercise is apparent in SkBF (Figure 3). After nicotinic acid ingestion, this vasoconstrictor response at the onset of exercise was not as apparent as skin blood flow is increasing before exercise starts. In this situation, the balance between vasodilation and vasoconstriction was different than normal exercise and more analogous to initiation of exercise when the skin is already hot. Experiments by Taylor *et al.* (1984) showed that vasoconstriction associated with initiation of exercise was not prominent when the skin is already hot.

Nicotinic acid ingestion before semi-upright ergometric exercise resulted in reduced heat storage during 30 min of exercise in a slightly warm environment. This observation superficially indicates that nicotinic acid could be used as a thermoregulatory aid to decrease heat storage during exercise. However, several additional factors must be considered before it can determined whether nicotinic acid can safely be used in this application. First, nicotinic acid decreases mobilization of free fatty acids in humans (Doi *et al.*, 1979) which may adversely affect energy production necessary for prolonged exercise. In this study, we did not detect a difference in metabolic rate (indirect calorimetry) during exercise between the control and nicotinic acid experiments. However, after nicotinic acid ingestion there were complaints from the subjects of fatigue and sleepiness, particularly after the resting experiments. Second, the mode of exercise must be considered as posture affects hydrostatic pressure which directly affects skin blood flow (Johnson, 1986; Rowell, 1986). Because exercise was done in the semi-upright posture in this study, the

conclusions from the current investigation cannot be indiscriminately applied to exercise in the upright posture. Third, the ambient environmental conditions must be considered. To effectively increase sensible heat flux after nicotinic acid the ambient dry bulb temperature must be less than skin temperature. In an environment where mean skin temperature is equal to the ambient dry bulb temperature, higher blood flow will not increase sensible heat flux from the skin to the environment. Finally, the dose of nicotinic acid was very low (300-400 mg) in this study compared to the therapeutic dose used to treat hypercholesterolemia (Brown and Goldstein, 1985). The dose of NA used in this study was great enough to cause increased vasodilation during exercise (30 min) in the individuals studied.

Upright Exercise and Clothing Study

In this study physiologic responses during heat stress in men and women wearing a chemical protective clothing system during exercise are described. The ingestion of niacin decreased heat storage during exercise by increasing sensible or dry heat loss, particularly from the chest and the arms during treadmill walking. This occurred without significant negative effects on cardiovascular parameters measured. The wearing of a chemical protective clothing system increased blood flow to the skin as indicated by higher skin temperatures than observed in a similar environment when wearing athletic clothing. Water loss via sweat secretion is also greater when wearing a clothing system that is relatively impermeable to water vapor. Both responses exacerbated cardiovascular strain. Protective clothing systems of this type compromise thermoregulatory heat loss by decreasing the transfer of heat from the body surface via the biophysical properties of convection and evaporation. Yet, the subjects were able to complete the thirty minutes of moderate exercise even though cardiovascular strain occurred during upright exercise (Table 5).

Due to the clothing worn and the environmental conditions imposed by the study, little dry heat flux was possible due to the small temperature gradient between the skin and the clothing, the small temperature gradient between the clothing and the ambient air and the relatively high thermal resistance of the clothing system. Therefore, the combination of the environmental conditions and the moderate work intensity did not allow significant dry heat flux through the clothing during the control

experiment. Since heat loss in warm environments during exercise is primarily via evaporative heat loss, the resistance of a clothing system to transmission of water vapor is critical to the length of time an individual can perform a specific task. The wearing of relatively non-porous clothing, such as that worn by our subjects, provides such a resistance to the transmission of water vapor. However in the niacin experiments, higher skin temperatures resulting from increased skin blood flow increased sensible heat loss through the clothing attenuated the increase in core temperature during exercise.

Early studies of heat transfer through clothing layers (flat plate, thermal mannikin, or human studies), have provided descriptors of factors which attenuated heat transfer from man to his environment. For example, the ratio of i_m/Clo gives an estimate of expected evaporative heat transfer through a clothing system (MOPP II). In this study, the ratio 0.28 estimates that 28% of secreted sweat (and possible evaporative heat transfer) should occur through the clothing system. There was no difference in sweating rate between the niacin and the control experiments. The difference in core temperature (i.e. lower in niacin experiments) may be due to possible pumping through the neck of the clothing system ("chimney effect"; Gonzalez and Cena, 1985), and perhaps not due to heat transfer through the clothing system.

In summary, exercise was done in an upright posture in this study with no significant cardiovascular difficulties encountered. However, in an environment where mean skin temperature was equal to or less than the ambient dry bulb temperature, higher blood flow would not increase sensible heat flux from the skin to the environment and may in fact, result in greater cardiovascular strain than observed during light to moderate exercise in the moderately warm conditions of this study. Finally, the dose of nicotinic acid was very low (300-400 mg) in this study compared to the therapeutic dose used to treat hypercholesterolemia (Brown and Goldstein, 1985). It is not known whether a higher dose would have a similar efficacy in stimulating sensible heat flux or whether a higher dose might adversely affect exercise capacity.

CONCLUSIONS

In summary, pharmacological manipulation of skin blood flow at rest and during moderate exercise was done by nicotinic acid ingestion. This method effectively increased sensible heat flux during seated as well as upright exercise. NA ingestion also increased sensible heat flux from individuals dressed in chemical protective clothing. These conclusions are limited to the environmental conditions used in these experiments, the time of day when the experiments were done, and to the relatively short duration (30 min) of exercise. Further research into the use of NA as a vasodilatory aid should concentrate on titrating circadian effects of NA. In addition, NA ingestion might be useful to help determine dynamic circadian responses of skin blood flow and the contribution of skin blood flow to blood pressure regulation. Finally, these experiments show that pharmacologic manipulation of skin blood flow by NA ingestion should be done cautiously, especially when NA will be used repeatedly or in novel circumstances.

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